

TABLE 1.—SUBCHRONIC, CHRONIC, AND OTHER TOXICITY—Continued

Guideline No.	Study Type	MRID No. (year)/Classification/Doses	Results
870.7485	Metabolism and pharmacokinetics rat	43492844 (1994) Acceptable/guideline 20, 200 mg/kg/day	Low recoveries of the radioactive dose in urine and tissues indicate limited absorption of CL 303,630 (chlorfenapyr) by rats. The radioactivity in urine, as a percent of administered dose, from the high dosed rats was about half that from the single and multiple-low dosed rats. More than 80% of the doses were eliminated in the feces. Most of the radioactivity was eliminated in the feces and urine within 48 hours of dosing. After 7 days, 89–121% of the dosed radioactivity was recovered. At sacrifice, female rats had greater (about twice) recovery of radioactivity in the carcass, blood, and fat at all doses than did males. The highest recovery of radioactivity from a single organ was from the liver (0.15–0.48% of dose). Metabolite and parent compound accounted for 72–91% of the radioactive doses. Parent compound was the major radioactive component found in excreta, accounting for approximately 40–70% of the administered doses. Minor amounts of eight primary and conjugated metabolites and four unidentified isolated components were detected, each at less than 10% of the dosed radioactivity. Liver and kidney contained several primary and conjugated metabolites and only minor levels of the parent compound ( $\leq 8.3\%$ of the radioactivity in the sample). Based on the metabolites identified, the major deposition route of orally administered chlorfenapyr is fecal excretion of unaltered parent compound. Other pathways include cleavage of the ethoxymethyl side-chain, followed by de-alkylation and ring hydroxylation, and some degree of conjugation of the de-alkylated, ring-hydroxylated metabolite. The two rings of the molecule are not cleaved. Metabolites are excreted primarily in urine; accumulation in tissues is minimal.

### B. Toxicological Endpoints

The dose at which the NOAEL from the toxicology study identified as appropriate for use in risk assessment is used to estimate the toxicological level of concern (LOC). However, the LOAEL is sometimes used for risk assessment if no NOAEL was achieved in the toxicology study selected. An uncertainty factor (UF) is applied to reflect uncertainties inherent in the extrapolation from laboratory animal data to humans and in the variations in sensitivity among members of the human population as well as other unknowns. An UF of 100 is routinely used, 10X to account for interspecies differences and 10X for intraspecies differences. An additional safety factor (SF) may be required if the data base is

incomplete. For chlorfenapyr EPA concluded that a developmental neurotoxicity (DNT) study is required based on the presence of neuropathology (CNS lesions) and neurotoxic signs seen in adult rats (males) and mice (both sexes). EPA further concluded that a UF of 10X is required until the data are received and evaluated. EPA does not have sufficient reliable data justifying the selection of a factor lower than the default 10X value for the additional SF for the protection of infants and children for this data gap.

For dietary risk assessment (other than cancer) the Agency uses the UF to calculate an acute or chronic reference dose (acute RfD or chronic RfD) where the RfD is equal to the NOAEL divided by the appropriate UF ( $\text{RfD} = \text{NOAEL} / \text{UF}$ ). Where an additional SF is retained

due to concerns unique to the FQPA, this additional factor is applied to the RfD by dividing the RfD by such additional factor. The acute or chronic Population Adjusted Dose (aPAD or cPAD) is a modification of the RfD to accommodate this type of FQPA SF.

For non-dietary risk assessments (other than cancer) the UF is used to determine the LOC. For example, when 100 is the appropriate UF (10X to account for interspecies differences and 10X for intraspecies differences) the LOC is 100. To estimate risk, a ratio of the NOAEL to exposures (margin of exposure (MOE) =  $\text{NOAEL} / \text{exposure}$ ) is calculated and compared to the LOC.

A summary of the toxicological endpoints for chlorfenapyr used for human risk assessment is shown in Table 2 of this unit:

TABLE 2.—SUMMARY OF TOXICOLOGICAL DOSE AND ENDPOINTS FOR CHLORFENAPYR FOR USE IN HUMAN RISK ASSESSMENT.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13–50 years of age)	NOAEL = 15 mg/kg UF = 1,000 aRfD = 0.015 mg/kg	Special FQPA SF = 1X aPAD = $\text{aRfD} \div \text{FQPA SF}$ = 0.015 mg/kg	Developmental toxicity study - rabbit LOAEL = 30 mg/kg/day based on increased post-implantation loss